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Welwitindolinone C synthetic studies. Construction of the welwitindolinone carbon skeleton via a transannular nitrone cycloaddition

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Abstract

Described is the construction of the *N*-methylwelwitindolinone C core via an efficient strategy that employs a sequential rhodium carbenoid-mediated O–H insertion, Claisen rearrangement and transannular [3+2] nitrone cycloaddition.

Keywords

Welwitindolinone; [3+2] Dipolar cycloaddition; Rhodium carbenoid; O–H insertion; Chloronium-ion semi-pinacol

1. Introduction

Since their isolation in 1994 from the cyanobacteria *Hapalosiphon welwitschii* and *Westiella intricate*, the welwitindolinone alkaloids have received significant attention from the synthetic community.[1–18] Of biological relevance, it was found that *N*-methylwelwitindolinone C isothiocyanate (**1**) was responsible for the P-glycoprotein-mediated MDR-reversing and larvacidal activities associated with the algae extracts.[19,20] Intrigued by its structural complexity and promising biological activity, we initiated a program for the total synthesis of **1**. Our initial attempt (Path A, Scheme 1), reported in 1999, highlighted the utility of Montmorillonite K-10 clay in a rhodium catalyzed C–H aryl insertion reaction that provided access to key α-diazo ketone **4**. Subsequent O–H insertion chemistry produced enol ether **3**, which was further elaborated to the welwitindolinone core (**2**) in 4 steps. Unfortunately, numerous attempts to install the bridgehead nitrogen failed;[21] thus an alternate strategy was devised. Herein we report the details of this approach (Path B, Scheme 1) which calls for the preparation of intermediate isoxazolidine **7** via a nitrone-mediated transannular [3+2] dipolar cycloaddition of olefin **6**.[22,23–26] Taking maximum advantage of our prior efforts, olefin **6** was seen as arising from the previously prepared diazoketone **4** by employing a two-step sequence involving rhodium-catalyzed O–H insertion/ring-opening to deliver enol ether **5** followed by Claisen rearrangement.[4,27,28]

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Dedicated to Professor Steven Ley, a friend and inspirational leader in organic chemistry.

2. Results and discussions

As previously reported,[4] diazoketone **4** was efficiently accessed from isatin (**8**) as outlined in Scheme 2. In the event **8** was converted to carboxylic acid **11** by a three-step sequence involving Wittig olefination (**8** → **9**), phosphonium ylide-induced cyclopropanation–*N*-alkylation (**9** → **10**), and hydrolysis of the resultant ethyl ester (**10** → **11**). Subsequent acid chloride formation and treatment with trimethylsilyl diazomethane provided the desired α-diazo ketone **12**. After an extensive catalyst screen, it was found that $Rh_2(TFA)_4$ in the presence of Montmorillonite K-10 clay optimally promoted the aryl C–H insertion reaction to provide tetracycle **13**. Benzylic oxidation of ketone **13** and regioselective diazotization afforded diazoketone **4**.

With ready access to α-diazoketone (**4**) and taking inspiration from early reports by Funk,[22] we turned toward the transannular nitrone cycloaddition (Scheme 3). In initial studies we targeted model substrate **15** and thus began with the Rh(II)-promoted coupling of **4** with allyl alcohol. In the event, sequential O–H insertion/cyclopropane ring-opening furnished known enol ether **14**.[4] Subsequent Claisen rearrangement under thermal conditions provided the desired diketone (**15**) as a an initial 1:1 mixture of diastereomers that underwent equilibration to the illustrated *single* diastereomer upon silica gel chromatography.

Having installed the pendant olefin, we were poised for the proposed cycloaddition and were delighted to find that exposure of **15** to *N*-methylhydroxylamine and pyridine in methanol at reflux regioselectively furnishes a nitrone (observed but not isolated) which, in turn, undergoes [3+2] cyloaddition to produce **16** in 81% yield. Although this single-step procedure established the viability of the transannular cycloaddition for installing the requisite bridgehead nitrogen, issues of ring size, cleavage of the N–O bond, and nitrogen deprotection remained. Regarding the latter, the use of *N*-benzyl hydroxylamine (Scheme 4) is representative of several variations which were explored and found to either resist cycloaddition or give large amounts of oxazole side-products via dehydration of the intermediate nitrone (i.e., **18**).[29,30] Eventually a more satisfactory solution that allowed advancement of the *N*-methylhydroxylamine adducts was implemented (*vide infra*).[23,24,31,25,26]

Turning to the issue of ring size, we targeted intermediate **21**, a compound that was both accessible via the developed O–H insertion/ring-opening/Claisen rearrangement cascade and poised for an olefin transposition that would set the stage for cycloaddition to the requisite six-membered ring of **1** (Scheme 5). Implementation of this plan began with the combination of diazoketone **4** and alcohol **19** in the presence of $Rh_2(OAc)_4$.[32] The derived enol ether **20** was subjected to thermally-induced Claisen rearrangement conditions to provide acetate **21** which was isolated as a *single* isomer after purification.[33] Palladium-catalyzed allylic transposition of **21** to the contra-thermodynamic terminal alkene **22** was followed by the key [3+2] dipolar cycloaddition.[34,35] To our delight, exposure of diketone **22** to *N*-methylhydroxylamine in EtOH at reflux gave isoxazolidine **23** as a complex mixture of diastereomers; thus, completing assembly of the welwitindolinone core.[36]

Although success in accessing **23** further established the O–H insertion/Claisen rearrangement sequence as quite general and illustrated the feasibility of accessing both the bridghead nitrogen and six-membered ring, inefficiencies associated with the olefin transposition led us to briefly explore alternatives. To this end, it was envisioned that replacing **19** with alcohol **24** would allow us to avoid the olefin transposition and provide a more functionalized isoxazolidine (Scheme 6).[37–39] As illustrated, exposure of diazoketone **4** to alcohol **24** in the presence of $Rh_2(OAc)_4$ produced enol ether **25**, which was converted to diketone **26** upon heating. However, subsequent treatment of diketone **26** to our established cycloaddition conditions failed to provide desired cycloadduct **27**. Instead, cyclization of the intermediate nitrone (not shown) onto the 1,1-disubstituted olefin converted diketone **26** exclusively to adduct **28**, the structure of which was confirmed by X-ray crystallography.[40] Attempts to modify the chemoselectivity of the cycloaddition by removal of the trimethylsilyl group or by olefin functionalization were unsuccessful.

Although the selectivity observed in the cycloaddition of **26** was disappointing we were encouraged by our ability to stereoselectively forge the fully-substituted quaternary carbon adjacent to the bridgehead nitrogen and thus began pursuing an alternative wherein the requisite [4.3.1] bicyclic backbone and C12 quaternary center would be produced in a single step (Scheme 7). The designed cyclization substrate in this scenario (**33**) was prepared in a sequence that began with cross metathesis of diketone **15** and silyl ether **29** followed by silyl deprotection.[41,42] The derived alcohol (**30**) was isolated as an inconsequential mixture of *E/Z* diastereomers (2:1, respectively). Selenenylation of **30** via the method of Grieco [*o*-$(NO_2)C_6H_4$-SeCN and P(*n*-Bu)$_3$] furnished selenide **31** which,[43–45] upon oxidation with DMDO provided the corresponding epoxy selenoxide. As expected the latter was unstable and upon work-up underwent clean elimination to deliver vinyl epoxide **32** in good yield.[46,47]

Having accessed **32**, attention was turned to opening the epoxide and delivering the cycloaddition substrate (**33**). After considerable fruitless experimentation with several Lewis acids we eventually explored a palladium-catalyzed isomerization approach pioneered by Noyori[48] and modified more recently by Radinov.[49] Under the latter conditions, opening of vinyl epoxide **32** in the presence of a fluorinated alcohol proceeded to furnish hemiacetals **33**α and **33**β as an inseparable mixture of diastereomers. Although the intermediacy of the hemiacetals was expected, the effect of the altered electronics on the subsequent cycloadditon was uncertain (cf., **26** and **33**). Unfortunately, exposure of **33**α and **33**β to *N*-methylhydroxylamine under forcing conditions did not produce any of the desired cycloadduct **34**.

In addition to our efforts with the more advanced cycloaddition substrates illustrated in Schemes 6 and 7, we had continued exploring cycloadduct **23** as a potential intermediate (Scheme 8). In these more fruitful studies, recent results from our synthetic approach to welwitindolinone A (**35**) were most influential and we targeted allylic alcohol **38** as an eventual substrate for a chloronium-ion induced semi-pinacol rearrangement that was envisioned as giving rise to the desired quaternary center and requisite neopentyl chlorine.[11,13,50]

As illustrated in Scheme 9, isoxazolidine **23** was advanced by first rearranging to the corresponding aminal (**39**).[26,51] Subsequent treatment of **39** with hydroxylamine hydrochloride produced amino-alcohol **40** in 95% yield. To set the stage for eventual introduction of the bridgehead isonitrile, **40** was bis-fomylated.[52,53] Selective deformylation of the derived formate produced alcohol **41** which, in a three-step process involving oxidation with Dess–Martin periodinane (DMP),[54] base-induced elimination to the enal, and addition of methyl magnesium bromide, was converted to secondary alcohol **42** as an inconsequential mixture of diastereomers. In practice, the instability to silica gel of the intermediates produced in this three-step sequence required that it be performed without purification. Finally, oxidation of alcohol **42** to enone **43**, followed by addition of methyl magnesium bromide, provided desired tertiary allylic alcohol **38**, albeit in low yield.

Despite its poor overall yield, the unoptimized synthetic sequence leading to **38** provided sufficient material to explore the proposed halonium ion induced semi-pinacol rearrangement. In the event, exposure of **38** to $CeCl_3$ $7H_2O$ and NaOCl was found to produce **44**. Extensive NMR analysis indicated that chloronium ion activation resulting in rearrangement had occurred from what appeared to be the desired and sterically more demanding face. However this transformation was accompanied by over-chlorination. Given our success in applying this type of semi-pinacol in the welwitindolinone A synthesis (Scheme 8) we were both surprised and dissappointed.[11,13] In recent efforts to overcome this problem, preliminary studies wherein the stoichiometry of the oxidant is limited have revealed that in substrate **38** the aromatic system reacts first. Thus, as is often the case with synthetic endeavors, the absence of a simple solution has inspired further efforts and the completion of **1** continues to challenge our resolve.

3. Conclusion

In summary, we have developed a novel approach toward the synthesis of *N*-methylwelwitindolinone C isothiocyanate (**1**) that employs a sequential O–H insertion/Claisen rearrangement followed by a transannular [3+2] nitrone cycloaddition to efficiently deliver a heavily functionalized carbocyclic welwitindolinone core (**23**). Further advancement of **23** via a chloronium-ion induced semi-pinacol rearrangement allows installation of the requisite quaternary center; however, over functionalization in this process has to-date thwarted efforts to complete the synthesis. The exploration of alternative strategies for accessing **1** as well as optimization studies on reactions leading to **23** are currently underway.

4. Experimental

4.1. General

Unless otherwise stated, reactions were magnetically stirred in flame-dried glassware under an atmosphere of nitrogen. Triethylamine (Et_3N) and methanol were dried over calcium hydride. Benzene, tetrahydrofuran, dichloromethane, toluene, and diethyl ether were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. All other commercially available reagents were used as received.

Unless otherwise stated, all reactions were monitored by thin-layer chromatography (TLC) using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 μm). Column or flash chromatography was performed with the indicated solvents using Silicycle SiliaFlash® P60 (230–400 mesh) silica gel as the stationary phase. Chromatography was conducted in accordance with the guidelines reported by Still et al.[55] All melting points were obtained on a Gallenkamp capillary melting point apparatus and are uncorrected.

Infrared spectra were obtained using a Midac M1200 FTIR or a Nicolet Avatar 320 FTIR. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-500, Bruker Avance DPX-500, Bruker Avance DPX-400, or Varian Inova 400 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to internal residual solvent peaks from indicated deuterated solvents. High-resolution mass spectra were performed at the University of Illinois Mass Spectrometry Center or by Donald L. Dick of Colorado State University. Single-crystal X-ray analyses were performed by Susan DeGala of Yale University.

4.1.1. Diketone 15—To a solution of diazo ketone **4** (630 mg, 2.36 mmol, 1.0 equiv) and allyl alcohol (161 μL, 2.36 mmol, 1.0 equiv) in CH_2Cl_2 (24 mL) was added $Rh_2(OAc)_4$ (10.4 mg, 0.024 mmol, 0.01 equiv). Gas evolution was observed and the reaction turned dark brown. After stirring at rt for 20 minutes, the mixture was concentrated to afford a dark brown oil which was subsequently dissolved in xylenes (35 mL) and heated at reflux for 1 hour. After cooling to room temperature, the reaction was concentrated and purified by silica gel column chromatography (30% hexane/EtOAc) to afford diketone **15** as yellow crystals (596 mg, 85% yield). m.p. 196–197 °C; FTIR (thin film/NaCl) 3079, 2895, 1706, 1597, 1467, 1408, 1368, 1337, 1295, 1269, 1187, 1161, 1140, 1019 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 5.59 (dddd, *J* = 6.7, 6.7, 10.3, 17.0 Hz, 1H), 5.02–4.98 (m, 2H), 3.36 (s, 1H), 3.25 (s, 3H), 2.93 (dd, *J* = 2.4, 11.6 Hz, 1H), 2.74 (ddd, *J* = 6.9, 12.2, 13.2 Hz, 1H), 2.18 (ddd, *J* = 1.0, 6.4, 14.0 Hz, 1H), 1.50 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 192.5, 174.3, 145.1, 134.8, 129.6, 129.1, 128.6, 120.7, 117.6, 113.3, 57.2, 53.0, 38.4, 29.9, 26.4, 22.7, 20.9; HRMS (EI) *m/z* 297.1364 [calc'd for $C_{18}H_{19}NO_3$ (M+) 297.1365].

4.1.2. Isoxazolidine 16—To a solution of diketone **15** (386 mg, 1.30 mmol 1.0 equiv) in MeOH (15 mL) was added *N*-methylhydroxylamine hydrochloride (543 mg, 6.50 mmol, 5.0 equiv) followed by pyridine (736 μL, 9.10 mmol, 7.0 equiv). The reaction mixture was heated at reflux for 15 hours and was concentrated after cooling to room temperature. The residual pyridine was removed *in vacuo* and the crude white solid was redissolved in EtOH (18 mL) and imidazole hydrochloride was added (272 mg, 2.60 mmol, 2.0 equiv). The mixture was heated at reflux for an additional 14 hours. After cooling to room temperature, the reaction was concentrated and purified by silica gel column chromatography (30% hexane/EtOAc) to furnish cycloadduct **16** as white crystals (342 mg, 81% yield). m.p. 206–207 °C; FTIR (thin film/NaCl) 2964, 2928, 2872, 1709, 1593, 1588, 1468, 1368, 1334, 1300, 1210, 1169, 1146, 1115, 1077, 1008 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, *J* = 8.2 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 3.99 (dd, *J* = 6.5, 8.7 Hz, 1H), 3.77 (d, *J* = 8.8 Hz, 1H), 3.49 (s, 1H), 3.28 (m, 1H), 3.23 (s, 3H), 3.19 (s, 3H), 2.61 (dd, *J* = 9.7, 14.1 Hz, 1H), 2.38 (d, *J* = 8.3 Hz, 1H), 1.97 (ddd, *J* = 8.7, 8.7, 14.1 Hz, 1H), 1.58 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8, 175.0, 144.5, 135.1, 128.9, 123.6, 117.3, 106.8, 76.4, 73.1, 65.3, 52.4, 51.7, 42.2, 39.7, 28.8, 26.3, 25.1, 21.4; HRMS (EI) *m/z* 326.1627 [calc'd for $C_{19}H_{22}N_2O_3$ (M+) 326.1630].

4.1.3. Isoxazolidine 17 and Oxazole 18—To a solution of diketone **15** (96 mg, 0.32 mmol, 1.0 equiv.) in MeOH (5 mL) was added *N*-benzylhydroxylamine hydrochloride (258 mg, 1.62 mmol, 5.0 equiv.) followed by pyridine (131 μL, 1.62 mmol, 5.0 equiv.). The reaction mixture was heated at reflux for 15 hours and was concentrated after cooling to room temperature. The residual pyridine was removed *in vacuo* and the crude white solid was redissolved in EtOH (8 mL) and imidazole hydrochloride was added (34 mg, 0.32 mmol, 1.0 equiv.). The mixture was heated at reflux for an additional 18 hours. After cooling to room temperature, the reaction was concentrated and purified by silica gel column chromatography (30% hexane/EtOAc) to afford oxazole **18** as a white solid (50 mg, 40% yield) and cycloadduct **17** as a white solid (62 mg 48% yield). **17:** m.p. >243 °C; FTIR (thin film/NaCl) 2969, 2924, 2873, 1739, 1697, 1608, 1592, 1470, 1368, 1341, 1304, 1149, 1080, 1012, 986, 910, 774, 728, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.7 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.30 (m, 2H), 7.06 (d, *J* = 7.9 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 4.89 (d, *J* = 16.4 Hz, 1H), 4.52 (d, *J* = 16.5 Hz, 1H), 4.02 (dd, *J* = 6.8, 8.6 Hz, 1H), 3.78 (d, *J* = 8.6 Hz, 1H), 3.55 (s, 1H), 3.32 (dd, *J* = 9.0, 15.6 Hz, 1H), 3.21 (s, 3H), 2.66 (dd, *J* = 10.0, 14.4 Hz, 1H), 2.45 (d, *J* = 8.5 Hz, 1H), 2.03 (ddd, *J* = 8.6, 8.6, 14.4 Hz, 1H), 1.62 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.4, 175.1, 144.6, 139.4, 135.0, 129.1, 128.4, 127.5, 126.9, 123.7, 117.4, 106.9, 76.6, 73.6, 65.1, 55.3, 51.9, 51.7, 42.2, 28.9, 26.3, 25.1, 21.5; HRMS (FAB) *m/z* 403.2022 [calc'd for $C_{25}H_{27}N_2O_3$ (M+1) 403.2022]. **18:** m.p. 156–157 °C; FTIR (thin film/NaCl) 2930, 1707, 1618, 1600, 1464, 1372, 1337, 1299, 1083, 915, 784 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (m, *J* = 1.7, 8.0 Hz, 2H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.51-7.47 (m, 3H), 7.41 (t, *J* = 7.9 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 5.91 (dddd, *J* = 6.3, 8.4, 10.3, 16.8 Hz, 1H), 5.10-5.03 (m, 2H), 3.74 (s, 1H), 3.25 (s, 3H), 3.00 (dd, *J* = 4.2, 7.4 Hz, 1H), 2.90 (m, 1H), 2.49 (ddd, *J* = 7.4, 7.6, 14.7 Hz, 1H), 1.68 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 160.0, 150.6, 143.8, 136.3, 133.5, 130.2, 128.8, 128.2, 128.1, 127.5, 126.3, 122.7, 119.1, 116.9, 106.6, 50.4, 50.1, 38.2, 34.2, 26.4, 25.9, 24.9; HRMS (EI) *m/z* 384.1839 [calc'd for $C_{25}H_{24}N_2O_2$ (M+) 384.1838].

4.1.4. Acetate 21—To a solution of diazo ketone **4** (6.00 g, 22.4 mmol, 1.0 equiv.) and allylic alcohol **19** (3.50 g, 26.9 mmol, 1.2 equiv.) in CH_2Cl_2 (224 mL) at room temperature was added $Rh_2(OAc)_4$ (250 mg, 0.56 mmol, 0.02 equiv.). As soon as gas evolution ceased (ca. 1 minute), Et_3N (15.6 mL, 112 mmol, 5.0 equiv.) was quickly added at once *via* syringe. The mixture was concentrated to afford a dark purple oil which was subsequently dissolved in xylenes (224 mL) and heated at reflux for 45 minutes. After cooling to room temperature, the reaction was concentrated and purified by silica gel column chromatography (20% acetone/hexanes) to afford diketone **21** as a yellow solid (5.36 g, 65% yield). m.p. 170–172 °C; FTIR (thin film/NaCl) 2971, 2939, 2885, 1716, 1603, 1472, 1372, 1339, 1300, 1268, 1233 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d$_6$) δ 7.63 (d, *J* = 7.9 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 5.55-5.46 (m, 2H), 4.40 (dd, *J* = 3.6, 27.0 Hz, 1H), 4.37 (dd, *J* = 4.7, 27.0 Hz, 1H), 3.30 (s, 1H), 3.22 (s, 3H), 2.89 (dd, *J* = 2.3, 11.5 Hz, 1H), 2.72 (m, 1H), 2.17-2.13 (m, 1H), 2.00 (s, 3H), 1.45 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 193.3, 174.9, 170.6, 146.5, 132.6, 130.4, 130.0, 129.8, 127.9, 120.6, 114.4, 64.7, 57.9, 53.6, 263–38.9, 29.1, 26.5, 22.9, 21.1, 20.7; HRMS (EI) *m/z* 369.1571 [calc'd for $C_{21}H_{23}NO_5$ (M+) 369.1576].

4.1.5. Acetates 22—To a solution of a acetate **21** (4.25 g, 11.5 mmol, 1.0 equiv) in THF (115 mL) was added $PdCl_2(MeCN)_2$ (119 mg, 0.46 mmol, 0.04 equiv) and the reaction was warmed to 50 °C. After stirring for 2 hours, the reaction was cooled to room temperature, concentrated, adsorbed onto SiO_2 and subjected to flash chromatography (30% EtOAc/hexanes) to provide a 1:1.4 ratio of diastereomers of olefins **22a** and **22b** (1.20 g, 28% yield, 96% yield based on recovered starting material) and recovered acetate **21** (3.00 g, 71% yield). **22a:** Although the mixture will be carried on in the next step, separation of the minor diastereomer (**22a**) can be affected *via* recrystallization from EtOAc/hexanes: m.p. 194–195 °C; FTIR (thin film/NaCl) 2974, 2938, 1716, 1603, 1473, 1372, 1339, 1299, 1271, 1234, 1018 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.51 (dd, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 5.66 (ddd, *J* = 6.3, 10.6, 17.1 Hz, 1H), 5.19-5.14 (m, 2H), 5.04 (ddd, *J* = 4.8, 4.8, 9.4 Hz, 1H), 3.34 (s, 1H), 3.25 (s, 3H), 2.83 (d, *J* = 10.6 Hz, 1H), 2.46 (ddd, *J* = 10.0, 10.0, 14.2 Hz, 1H), 2.06 (s, 3H), 1.76 (dd, *J* = 4.1, 14.2 Hz, 1H), 1.47 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 192.4, 174.3, 170.5, 145.0, 135.4, 129.7, 129.1, 128.3, 120.6, 117.6, 113.3, 74.1, 53.9, 52.7, 38.5, 30.9, 26.4, 22.5, 21.2, 20.5; HRMS (EI) *m/z* 369.1586 [calc'd for $C_{21}H_{23}NO_5$ (M+) 369.1576]. **22b:** m.p. 97–99 °C (wax); FTIR (thin film/NaCl) 2972, 2939, 1717, 1603, 1472, 1373, 1339, 1299, 1271, 1233, 1022 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 5.58 (m, 1H), 5.29 (m, 1H), 5.12-5.09 (m, 2H), 3.35 (s, 1H), 3.25 (s, 3H), 2.93 (d, *J* = 11.1 Hz, 1H), 2.55 (ddd, *J* = 5.7, 11.2, 14.1 Hz, 1H), 2.07 (s, 3H), 1.67 (dd, *J* = 4.0, 14.1 Hz, 1H), 1.45 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 192.0, 174.4, 170.0, 144.9, 134.9, 129.6, 129.3, 128.2, 120.5, 117.3, 113.2, 71.9, 52.7, 51.6, 38.2, 30.0, 26.4, 22.4, 20.8, 20.5; HRMS (EI) *m/z* 369.1575 [calc'd for $C_{21}H_{23}NO_5$ (M+) 369.1576].

4.1.6. Isoxazolidines 23—*N*-Methylhydroxylamine hydrochloride (3.35 g, 40.1 mmol, 10.0 equiv.) was dissolved in EtOH (200 mL) *via* gentle heating with a heat gun. NaOMe (3.38 g, 40.5 mmol, 10.1 equiv.) was added, which resulted in immediate salt formation. The mixture was stirred for 2 hours and was then filtered into a round bottom flask containing acetates **22** (1.48 g, 4.01 mmol, 1.0 equiv.). The reaction was heated at reflux for 18.5 hours, which resulted in a complex mixture of products as visualized by NMR. After cooling to room temperature, the reaction was concentrated *in vacuo*, adsorbed onto SiO_2, and subjected to flash chromatography (30–75% EtOAc/hexanes). Three diastereomers were isolated and characterized as follows: **23a** and **23b:** (865 mg, 54% yield) FTIR (thin film/NaCl) 2968, 2933, 2878, 1744, 1708, 1603, 1592, 1464, 1368, 1339, 1300, 1235, 1143, 1118, 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.35-7.26 (m, 2H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 5.15 (m, 1H), 4.67 (ddd, *J* = 2.4, 10.0, 12.2 Hz, 1H), 4.27-4.09 (m, 3H), 3.83 (s, 1H), 3.74 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.43 (dd, *J* = 8.2, 17.8 Hz, 1H), 3.28 (s, 1H), 3.24-3.17 (m, 4H), 3.21 (s, 3H), 3.20 (s, 3H), 3.02 (s, 3H), 2.73 (dd, *J* = 8.8, 12.4 Hz, 1H), 2.64-2.58 (m, 3H), 2.24-2.16 (m, 1H), 2.11 (s, 3H), 2.02 (s, 3H), 1.86 (dd, *J* = 12.6, 25.0 Hz, 1H), 1.70 (s, 3H), 1.49 (s, 3H), 0.82 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0, 202.7, 174.8, 174.4, 170.3, 170.0, 144.5, 144.4, 136.4, 135.0, 129.1, 128.9, 124.1, 122.8, 122.2, 120.3, 107.4, 107.3, 80.3, 72.1, 71.6, 70.7, 69.6, 63.5, 61.5, 56.9, 54.9, 52.1, 49.0, 43.9, 40.0, 38.2, 38.1, 31.0, 30.2, 29.9, 26.4, 26.2, 24.6, 21.3, 21.0, 21.0, 19.4; HRMS (EI) *m/z* 398.1840 [calc'd for $C_{22}H_{26}N_2O_5$ (M+) 398.1842]. **23c:** (171 mg, 11% yield). FTIR (thin film/NaCl) 2967, 2882, 1738, 1713, 1603, 1462, 1370, 1340, 1308, 1233, 1054, 917, 787, 732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 5.23 (t, *J* = 4.7 Hz, 1H), 4.10 (t, *J* = 8.1 Hz, 1H), 3.69 (t, *J* = 9.1 Hz, 1H), 3.52 (ddd, *J* = 5.1, 8.0, 9.3 Hz, 1H), 3.34 (s, 1H), 3.18 (s, 3H), 2.71 (dd, *J* = 8.0, 12.1 Hz, 1H), 2.58 (s, 3H), 2.31 (ddd, *J* = 5.3, 8.2, 13.8 Hz, 1H), 2.07 (s, 3H), 1.81 (dd, *J* = 13.2, 13.2 Hz, 1H), 1.72 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 174.5, 170.2, 144.5, 135.8, 128.7, 123.9, 122.0, 107.1, 74.6, 66.5, 66.4, 63.8, 53.7, 52.5, 39.1, 36.9, 30.4, 29.7, 26.1, 20.8, 19.3; HRMS (EI) *m/z* 398.1851 [calc'd for $C_{22}H_{26}N_2O_5$ (M+) 398.1842].

4.1.7. Diketone 26—To a solution of diazo ketone **4** (115 mg, 0.43 mmol, 1.0 equiv.) and allylic alcohol **24** (66 mg, 0.43 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) was added $Rh_2(OAc)_4$ (1.9 mg, 0.004 mmol, 0.01 equiv.). Gas evolution was observed and the reaction turned dark brown. After stirring at rt for 30 minutes, the mixture was concentrated to afford a dark brown oil which was subsequently dissolved in xylenes (8 mL) and heated at reflux for 20 minutes. After cooling to room temperature, the reaction was concentrated and purified by silica gel column chromatography (30% hexane/EtOAc) to afford diketone **26** as yellow crystals (103 mg, 60% yield). m.p. 137–139 °C; FTIR (thin film/NaCl) 2966, 2900, 1705, 1599, 1469, 1411, 1370, 1338, 1295, 1268, 1251, 1082, 1022 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 5.36 (s, 1H), 5.28 (s, 1H), 3.39 (s, 1H), 3.32 (dd, *J* = 2.2, 11.0 Hz, 1H), 3.27 (s, 3H), 2.87 (dd, *J* = 11.2, 13.8 Hz, 1H), 2.27 (d, *J* = 14.1 Hz, 1H), 1.50 (s, 3H), 0.95 (s, 3H), 0.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.7, 191.7, 174.4, 145.0, 129.6, 129.4, 128.3, 128.2, 124.4, 120.8, 113.1, 104.1, 96.4, 56.0, 53.0, 38.4, 33.2, 26.4, 22.4, 20.9, −0.3; HRMS (EI) *m/z* 393.1756 [calc'd for $C_{23}H_{27}NO_3Si$ (M+) 393.1760].

4.1.8. Isoxazolidine 28—To a solution of diketone **26** (118 mg, 0.30 mmol, 1.0 equiv.) in MeOH (6 mL) was added *N* -methylhydroxylamine hydrochloride (126 mg, 1.50 mmol, 5.0 equiv.) followed by pyridine (171 μL, 2.10 mmol, 7.0 equiv.). The reaction mixture was heated at reflux for 15 hours and was concentrated after cooling to room temperature. The residual pyridine was removed *in vacuo* and the crude white solid was redissolved in EtOH (12 mL) and imidazole hydrochloride was added (63 mg, 0.60 mmol, 2.0 equiv.). The mixture was heated at reflux for an additional 14 hours. After cooling to room temperature, the reaction was concentrated and purified by silica gel column chromatography (25% EtOAc/hexane) to furnish cycloadduct **28** as white crystals (89 mg, 70% yield). m.p. 210–211 °C; FTIR (thin film/NaCl) 2967, 2928, 2873, 2172, 1736, 1708, 1606, 1589, 1467, 1386, 1338, 1299, 1250, 1214, 1172, 1106, 1084 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 4.09 (d, *J* = 8.3 Hz, 1H), 4.00 (d, J = 8.2 Hz, 1H), 3.96 (s, 1H), 3.28 (s, 3H), 3.16 (s, 3H), 2.71 (d, J = 14.4 Hz, 1H), 2.46-2.38 (m, 2H), 1.56 (s, 3H), 0.81 (s, 3H), −0.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.1, 175.0, 144.2, 132.1, 128.6, 125.0, 118.6, 107.2, 107.1, 90.7, 81.8, 64.4, 54.2, 52.8, 41.0, 39.3, 37.4, 26.1, 25.1, 21.8, 0.0; HRMS (EI) *m/z* 422.2018 [calc'd for $C_{24}H_{30}N_2O_3Si$ (M+) 422.2026].

4.1.9. Diketone 30—Diketone **15** (187 mg, 0.63, 1.0 equiv.) and olefin **29** (882 mg, 4.40 mmol, 7.0 equiv.) were diluted in CH_2Cl_2 (15.7 mL) and stirred for 10 minutes. Grubbs 2nd generation catalyst (54 mg, 0.063 mmol, 0.1 equiv.) was then added and the reaction was stirred at reflux overnight (approx. 12 hours). Upon completion as indicated by TLC, the reaction was concentrated and immediately purified via column chromatography (20% EtOAc/hexanes) to give the resulting coupled adduct (193 mg, 0.411 mmol). The coupled adduct was taken up in MeOH (41 mL) before pyridinium *p*-toluenesulfonate (21 mg, 0.082 mmol, 0.2 equiv.) was added. The reaction was stirred at room temperature over 12 hours whereupon TLC indicated the consumption of starting material. The reaction was concentrated, re-dissolved in EtOAc, washed with sat. $NaHCO_3$, brine, and dried over Na_2SO_4. Purification of the concentrated mixture by flash chromatography (50% EtOAc/hexanes) gave diketone product **30** (104 mg, *E/Z*: 2:1, 47% yield, 2 steps) as a yellow oil. FTIR (thin film/NaCl) 3420, 2935, 1715, 1604, 1473, 1372, 1339, 1300, 1272 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 2H), 7.29 (d, J = 7.6 Hz, 2H), 5.04-4.98 (m, 2H), 3.68-3.57 (m, 4H), 3.37 (s, 1H), 3.36 (s, 1H), 3.24 (s, 6H), 2.90-2.86 (m, 2H), 2.82-2.74 (m, 2H), 2.37-2.25 (m, 2H), 2.22-2.05 (m, 6H), 1.64 (s, 6H), 1.52 (s, 3H), 1.5 (s, 3H), 0.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9, 193.6, 174.5, 145.3, 135.2, 129.7, 129.0, 128.9, 124.2, 123.9, 120.92, 120.87, 113.5, 113.4, 60.6, 60.2, 58.3, 58.2, 53.4, 53.2, 43.0, 38.6, 38.3, 35.1, 26.6, 24.6, 24.5, 23.4, 23.0, 22.9, 21.3, 21.2, 15.9; HRMS (EI) *m/z* 356.1862 [calc'd for $C_{21}H_{26}NO_4$ (M+) 356.1856].

4.1.10. Selenide 31—A solution of alcohol **30** (60 mg, 0.17 mmol, 1.0 equiv.) in THF (1.69 mL) was treated with *o*-nitrophenylselenocyanate (46 mg, 0.20 mmol, 1.2 equiv.) at room temperature. The mixture was stirred for 10 minutes before tri-*n*-butylphosphine (50.5 μL, 0.20, 1.2 equiv.) was added. Upon completion as indicated by TLC (approx. 2 hours) an aliquot of sat. NH_4Cl was added. The resulting brown mixture was extracted with Et_2O, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the concentrated mixture by flash chromatography (30% EtOAc/hexanes) gave selenide **31** (49 mg, 54% yield) as a yellow oil. The major diastereomer was characterized as follows: FTIR (thin film/NaCl) 2970, 2930, 1716, 1604, 1513, 1473, 1332, 1303, 1271 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.58-7.49 (m, 3H), 7.31 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 5.02 (t, J = 7.2 Hz, 1H), 3.39 (s, 1H), 3.26 (s, 3H), 2.99-2.88 (m, 3H), 2.81 (ddd, J = 8.0, 13.2, 13.2 Hz, 1H), 2.39-2.35 (m, 2H), 2.15 (dd, J = 6.0, 13.6 Hz, 1H), 1.70 (s, 3H), 1.53 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6, 192.8, 174.5, 147.0, 145.2, 136.9, 133.8, 129.8, 129.3, 128.8, 126.6, 125.4, 122.9, 120.9, 113.4, 58.1, 53.3, 38.6, 38.2, 26.6, 24.6, 23.0, 21.2, 16.0; HRMS (EI) *m/z* 563.1060 [calc'd for $C_{27}H_{28}N_2NaO_5Se$ (M+) 563.1056].

4.1.11. Vinyl epoxide 32—In a flask open to air, selenide **31** (49 mg, 0.09, 1.0 equiv.) was diluted with CH_2Cl_2 (7 mL) and cooled to −78 °C. Freshly made dimethyldioxirane in acetone (7 mL, approx. 0.07–0.09 M) was added rapidly. The solution was stirred at −78 °C for 30 minutes and then gradually warmed to room temperature. The reaction was then concentrated *in vacuo* and subsequently purified by flash chromatography (20% EtOAc/hexanes eluent) to give diastereomeric vinyl epoxide **32** (23 mg, 72% yield) as a pale yellow solid. The mixture of diastereomers were characterized as follows: FTIR (thin film/NaCl) 2970, 1716, 1604, 1473, 1373, 1339, 1300, 1272 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72

(d, J = 8.0 Hz, 2H), 7.52 (t, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 5.82 (dd, J = 11.2, 17.6 Hz, 1H), 5.61 (dd, J = 10.8, 17.6 Hz, 1H), 5.29 (d, J = 17.2 Hz, 2H), 5.17 (d, J = 10.8 Hz, 2H), 3.39 (s, 1H), 3.38 (s, 1H), 3.25 (s, 6H), 3.14-3.10 (m, 2H), 2.70 (dd, J = 3.6, 8.4 Hz, 1H), 2.59 (dd, J = 4.0, 7.6 Hz, 1H), 2.47 (ddd, J = 4.0, 11.6, 13.6 Hz, 1H), 2.36 (ddd, J = 3.6, 11.6, 14.0 Hz, 1H), 1.59-1.53 (m, 2H), 1.49 (s, 3H), 1.45 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 0.93 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 192.1, 174.5, 145.2, 140.0, 135.5, 129.9, 129.3, 128.7, 121.1, 118.0, 116.5, 113.5, 63.4, 63.1, 62.1, 60.8, 54.7, 53.1, 38.8, 26.6, 25.4, 24.9, 22.8, 21.8, 21.1, 15.3; HRMS (EI) *m/z* 376.1526 [calc'd for $C_{21}H_{23}NNaO_4$ (M+) 376.1519].

4.1.12. Hemiacetals 33—Triphenylphosphine (20.0 mg, 75.0 μmol, 0.5 equiv.) and tris(dibenzylideneacetone)-dipalladium(0)-chloroform (7.0 mg, 7.5 μmol, 0.05 equiv) were combined and diluted with toluene (0.8 mL). The deep purple mixture changed to a deep yellow after 1 hour. 1,1,1,3,3,3-Hexafluoro-2-phenyl-2-propanol (25.3 μL, 0.15 mmol, 1.0 equiv.) was then added. After 10 minutes the mixture turned a deep red-orange and was added via cannula into a vial containing vinyl epoxide **32** (53.0 mg, 0.15 mmol, 1.0 equiv.) The reaction was then submerged in a 35 °C oil bath and left overnight (approx. 12 hours) to react. After completion as indicated by TLC, the reaction was rapidly concentrated and immediately purified by flash chromatography (20% EtOAc/hexanes) to give diastereomeric acetals **33** (31 mg, 58% yield) as an off white solid. The mixture of diastereomers was characterized as follows: FTIR (thin film/NaCl) 3377, 2926, 1699, 1604, 1372, 1339, 1298, 1216 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.0 Hz, 2H), 7.43 (t, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 6.46 (dd, J = 11.2, 18.0 Hz, 1H), 6.34 (dd, J = 11.6, 18.4 Hz, 1H), 5.45 (s, 1H), 5.3-5.02 (m, 8H), 4.72 (m, 1H), 4.14 (s, 1H), 4.08 (s, 1H), 3.24 (s, 3H), 3.23 (s, 3H), 3.03 (d, J = 11.6 Hz, 2H), 2.78 (m, 1H), 2.33-2.15 (m, 4H), 1.96-1.91 (m, 1H), 1.67 (s, 3H), 1.63 (s, 3H), 0.85 (s, 3H), 0.77 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 196.5, 175.9, 146.1, 145.9, 144.8, 136.5, 136.1, 131.3, 131.1, 129.0, 128.9, 127.9, 127.8, 122.2, 121.9, 114.7, 114.4, 114.2, 112.2, 112.1, 103.2, 102.6, 78.0, 75.9, 53.6, 52.7, 52.6, 50.5, 35.4, 35.2, 33.3, 31.1, 26.4, 25.3, 25.2, 23.8, 23.7; HRMS (EI) *m/z* 376.1519 [calc'd for $C_{21}H_{23}NNaO_4$ (M+) 376.1519].

4.1.13. Aminal 39—A 500 mL flask equipped with an addition funnel (containing 30 g 4 Å molecular sieves) and connected to a reflux condenser was charged with *p*-TSA (85 mg, 0.44 mmol, 1.0 equiv.) and benzene (150 mL). The resulting suspension was then heated at reflux for 1 hour before isoxazolidine **23** (175 mg, 0.44 mmol, 1.0 equiv.) was introduced as a solid in one portion. The resulting suspension was immersed into an oil bath and heated at 110 °C for 48 hours to provide a dark brown reaction mixture containing a small amount of a brown precipitate. The reaction was cooled to 0 °C and treated with Et_3N (61 μL, 0.44 mmol, 1.0 equiv.). Concentration provided a brown foam that was purified by silica gel chromatography (50–100% EtOAc/hexanes) to afford recovered starting material **23** (11 mg, 11%) and aminal **39** (94 mg, 54% yield, 65% BORSM) as a white solid. m.p. 251–254 °C; FTIR (thin film/NaCl) 2967, 1711, 1606, 1457, 1237 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (t, J = 8.1 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 4.60 (d, J = 10.7 Hz, 1H), 4.52 (d, J = 10.3 Hz, 1H), 4.34 (ddd, J = 5.0, 6.9, 12.5 Hz, 1H), 4.17 (dd, J = 5.5, 11.9 Hz, 1H), 3.35 (t, J = 12.1 Hz, 1H), 3.32 (s, 1H), 3.19 (s, 3H), 3.12-3.07 (m, 1H), 2.52 (dd, J = 7.6, 12.6 Hz, 1H), 2.16 (bs, 1H), 2.00 (s, 3H), 1.89-1.75 (m, 2H), 1.67 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 174.5, 170.3, 144.7, 139.6, 130.2, 123.6, 119.2, 107.8, 77.4, 69.9, 68.1, 66.1, 54.9, 51.3, 45.3, 39.2, 29.7, 28.8, 26.2, 21.1, 19.8; HRMS (EI) *m/z* 398.1839 [calc'd for $C_{22}H_{26}N_2O_5$ (M+) 398.1842].

4.1.14. Amino alcohol 40—A solution of aminal **39** (610 mg, 1.53 mmol, 1.0 equiv.) in MeOH (100 mL) was treated with hydroxylamine hydrochloride (1.06 g, 15.33 mmol, 10.0

equiv.). The solution that resulted was heated at reflux for 30 minutes before being cooled, concentrated, taken up in EtOAc (200 mL) and quenched with saturated $NaHCO_3$ (250 mL). Separation of the layers and extraction of the aqueous layer with EtOAc was followed by washing with brine, drying over Na_2SO_4, and concentration under reduced pressure. The resulting residue was purified using silica gel chromatography (30–100% EtOAc/hexanes) to furnish amino alcohol **40** (577 mg, 98% yield) as a white solid. m.p. dec. >205 °C; FTIR (thin film/NaCl) 3260, 2968, 1715, 1608, 1465, 1240, 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 4.32-4.27 (m, 1H), 3.58-3.47 (m, 2H), 3.18 (s, 3H), 3.16 (s, 2H), 2.63 (dd, *J* = 7.4, 12.0 Hz, 1H), 2.00 (s, 3H), 1.92-1.78 (m, 2H), 1.65 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 174.2, 170.4, 144.3, 141.1, 130.2, 121.7, 120.8, 107.4, 68.8, 67.2, 62.1, 54.9, 54.6, 51.3, 38.6, 29.3, 29.2, 26.1, 21.0, 19.6; HRMS (EI) *m/z* 386.1834 [calc'd for $C_{21}H_{26}N_2O_5$ (M+) 386.1842].

4.1.15. Alcohol 41—A solution of amino alcohol **40** (53 mg, 0.14 mmol, 1.0 equiv.) in THF (3.4 mL) at 0 °C was treated with freshly prepared acetic formic anhydride [0.52 mL, prepared by heating equal amounts of acetic anhydride (0.26 mL) and formic acid (0.26 mL) at 60 °C for 1 hour]. Stirring was continued for 5 minutes at this temperature and then at room temperature for 30 minutes. The reaction was then concentrated under reduced pressure. The crude mixture was then diluted in MeOH (3.4 mL) at room temperature and was treated with Et_3N (0.19 mL, 1.37 mmol, 10.0 equiv.). The solution was allowed to stir for 10 minutes, at which point TLC indicated complete consumption of starting material. Concentration *in vacuo* and purification by flash chromatography (100% EtOAc) furnished alcohol **41** (52 mg, 91% yield) as a pale yellow foam. m.p. 181–184 °C; FTIR (thin film/NaCl) 3300, 1730, 1694, 1609, 1466, 1236 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 2H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 4.62 (ddd, *J* = 5.5, 7.6, 12.5 Hz, 1H), 3.79-3.71 (m, 2H), 3.65 (s, 1H), 3.42 (dt, *J* = 3.0, 7.3 Hz, 1H), 3.18 (s, 3H), 2.60 (dd, *J* = 7.9, 12.1 Hz, 1H), 2.49 (t, *J* = 3.7 Hz, 1H), 2.01 (s, 3H), 1.90-1.78 (m, 2H), 1.67 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 175.1, 170.3, 160.2, 143.4, 138.0, 129.1, 124.9, 121.1, 107.3, 68.8, 68.6, 61.7, 55.1, 51.8, 51.7, 38.4, 29.2, 28.8, 26.1, 21.0, 20.0; HRMS (EI) *m/z* 414.1782 [calc'd for $C_{22}H_{26}N_2O_6$ (M+) 414.1791].

4.1.16. Alcohol 42—A solution of alcohol **41** (207 mg, 0.5 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) was treated with Dess-Martin periodinane (319 mg, 0.75 mmol, 1.5 equiv.) and stirred at room temperature for 30 minutes, at which point TLC indicated the reaction complete. The reaction was cooled to 0 °C before saturated $NaHSO_3$ (5 mL) and saturated $NaHCO_3$ (5 mL) were added. The two layers were separated and the organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude reaction mixture was diluted in CH_2Cl_2 (10 mL) and stirred at 0 °C before triethylamine (77 μL, 0.55 mmol, 1.1 equiv.) was added. After 30 minutes acetic acid (31 μL, 0.55 mmol, 1.1 equiv.) was added and the reaction was partitioned between CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ (20 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude reaction mixture, diluted in THF (10 mL) was cooled to 0 °C. A 3.0 M solution of methyl magnesium bromide in Et_2O (0.37 mL, 1.11 mmol, 3.0 equiv.) was added and the reaction was stirred for 30 minutes. Upon consumption of starting material, the reaction was quenched with 1 M NH_4Cl, extracted with EtOAc, washed with brine, and dried over Na_2SO_4. The resulting mixture was purified by flash chromatography (90% EtOAc/hexanes) to give secondary alcohol **42** as a mixture of diastereomers (134 mg, 73% yield, 3 steps). The complex mixture was carried through the next step and characterized.

4.1.17. Enone 43—A solution of alcohol **42** (20 mg, 0.05 mmol, 1.0 equiv.) in CH_2Cl_2 (1.9 mL) was treated with Dess-Martin periodinane (73 mg, 0.17 mmol, 3.0 equiv.) and stirred at room temperature for 8 hours, at which point TLC indicated the reaction complete. The reaction was cooled to 0 °C before saturated $NaHSO_3$ (2 mL) and saturated $NaHCO_3$ (2 mL) were added. The two layers were separated and the organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (75% EtOAc/hexanes) gave enone **43** (7 mg, 35% yield) as a pale yellow oil. FTIR (thin film/NaCl) 3329, 3055, 2970, 2917, 1731, 1698, 1609, 1465, 1368, 1340, 1266, 1243 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 1.2 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.04-7.02 (m, 1H), 6.9 (s, 1H), 6.70 (d, J = 8.0 Hz, 1H), 3.88 (s, 1H), 3.15 (s, 3H), 2.58-2.49 (m, 2H), 2.45 (s, 3H), 2.36-2.28 (m, 1H), 1.68 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 174.9, 160.1, 142.8, 134.6, 129.5, 126.0, 120.9, 107.2, 69.9, 51.8, 51.7, 37.7, 29.2, 27.8, 27.4, 26.3, 20.6; HRMS (EI) *m/z* 389.1480 [cacl'd for $C_{21}H_{22}N_2NaO_4$ (M +) 389.1472].

4.1.18. Allylic Alcohol 38—A solution of enone **43** (66 mg, 0.18 mmol, 1.0 equiv.) in THF (8 mL) was cooled to 0 °C. A 3.0 M solution of methyl magnesium bromide in Et_2O (0.30 mL, 0.90 mmol, 5.0 equiv.) was added and the reaction was stirred for 7 hours. Upon consumption of starting material, the reaction was quenched with 1 M NH_4Cl, extracted with EtOAc, washed with brine, and dried over Na_2SO_4. The resulting mixture was purified by flash chromatography (2% MeOH/$CHCl_3$) to give allylic alcohol **38** (26 mg, 26% yield) as a yellow oil.^1H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.02 (s, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 6.06 (s, 1H), 5.81-5.79 (m, 1H), 3.80 (s, 1H), 3.10 (s, 3H), 2.31-2.18 (m, 2H), 1.79-1.73 (m, 1H), 1.55 (s, 3H), 1.47 (s, 3H), 1.35 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 201.7, 174.5, 160.1, 147.3, 141.5, 136.4, 128.6, 125.3, 124.4, 121.1, 106.5, 73.0, 70.9, 51.3, 51.2, 36.5, 31.4, 30.2, 28.5, 25.8, 25.2, 19.8; HRMS (EI) *m/z* 405.1789 [calc'd for $C_{22}H_{26}N_2NaO_4$ (M+) 405.1785].

4.1.19. Chlorinated Product 44—Tertiary allylic alcohol **38** (51 mg, 0.133 mmol, 1.0 equiv.) was diluted in CH_3CN (10 mL) and stirred at 0 °C. Cerium(III) chloride heptahydrate (149 mg, 0.40 mmol, 3.0 equiv.) was added followed by addition of a 0.1 M aqueous solution of sodium hypochlorite (10.7 mL, 1.07 mmol, 8.0 equiv.). The reaction was stirred from 0 °C to room temperature over 9 hours whereupon TLC indicated consumption of starting material. The reaction was cooled to 0 °C before saturated sodium sulfite (10 mL) was added and stirred for 10 minutes. Chloroform was added and the layers were separated. The aqueous layer was extracted twice more with chloroform and the organic partitions were combine, washed with brine, and dried over Na_2SO_4. Purification of the filtrate by flash chromatography (33% EtOAc/hexanes) furnished chlorinated product **44** (49 mg, 71% yield) as a colorless foam. ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H) 7.41 (s, 1H), 5.03-4.98 (dd, J = 9.2, 11.6 Hz, 1H), 3.54 (s, 3H), 3.02 (s, 1H), 2.63-2.57 (dd, J = 9.6, 10.4 Hz, 1H), 2.53-2.45 (ddd, J = 8.8, 10.8, 14.0 Hz, 1H), 2.27 (s, 3H), 2.0 (s, 3H), 1.85-1.76 (ddd, J = 9.2, 11.4, 14.0 1H), 1.71 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 175.7, 171.7, 160.0, 140.3, 132.7, 132.6, 128.2, 127.4, 117.3, 90.3, 75.8, 60.8, 58.0, 54.4, 52.4, 40.6, 34.0, 30.1, 29.9, 26.8, 26.4, 26.0, 22.0, 21.4, 14.6, 14.5; HRMS (EI) *m/z* 541.0233 [calc'd for $C_{22}H_{22}Cl_4N_2NaO_4$ (M+) 541.0226].

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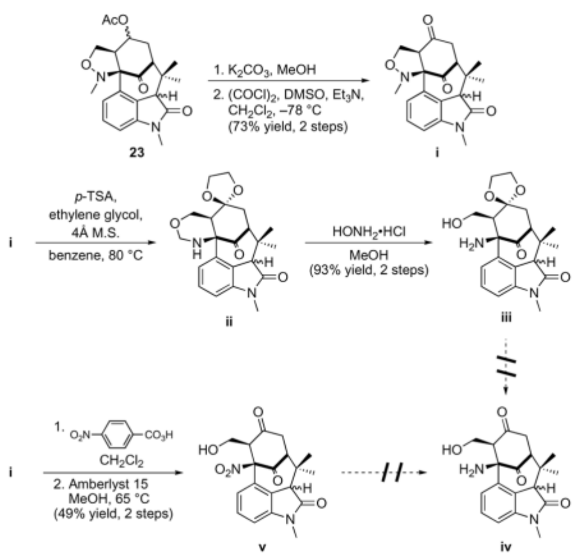

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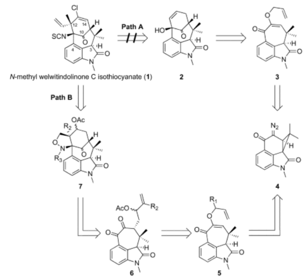
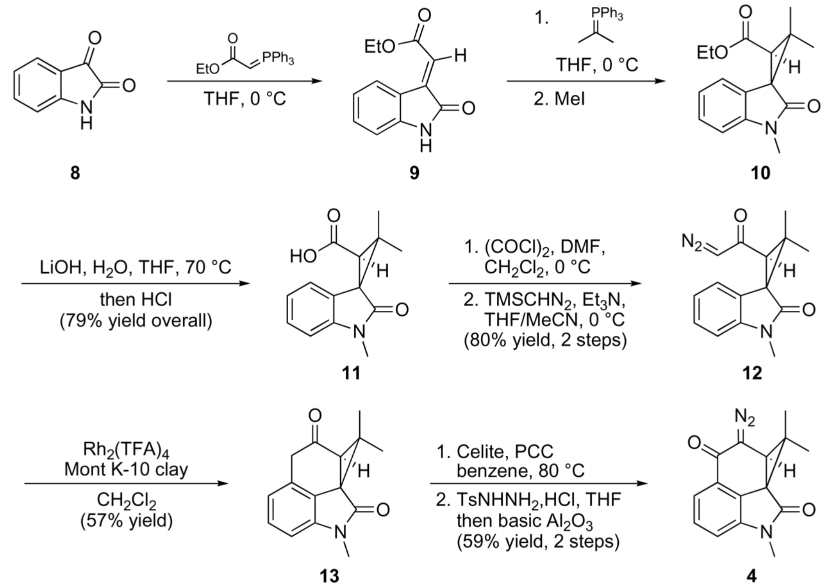
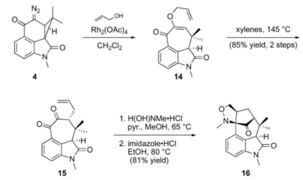


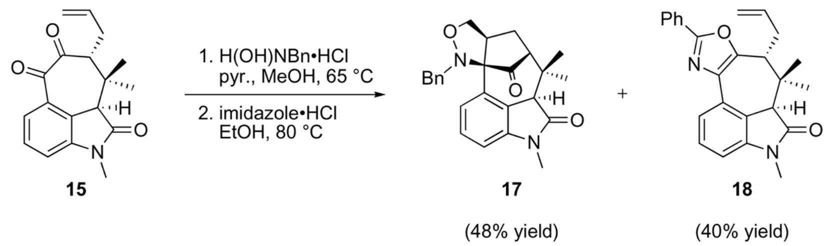
Scheme 1.
Retrosynthetic analysis


EtO
PPh3
THF, 0 °C
1. PPh3
THF, 0 °C
2. MeI
8
9
10
LiOH, H2O, THF, 70 °C
then HCl
(79% yield overall)
11
1. (COCl)2, DMF,
CH2Cl2, 0 °C
2. TMSCHN2, Et3N,
THF/MeCN, 0 °C
(80% yield, 2 steps)
12
Rh2(TFA)4
Mont K-10 clay
CH2Cl2
(57% yield)
13
1. Celite, PCC
benzene, 80 °C
2. TsNHNH2,HCl, THF
then basic Al2O3
(59% yield, 2 steps)
4

Scheme 2.

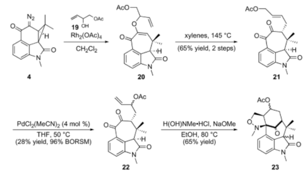


Scheme 3.

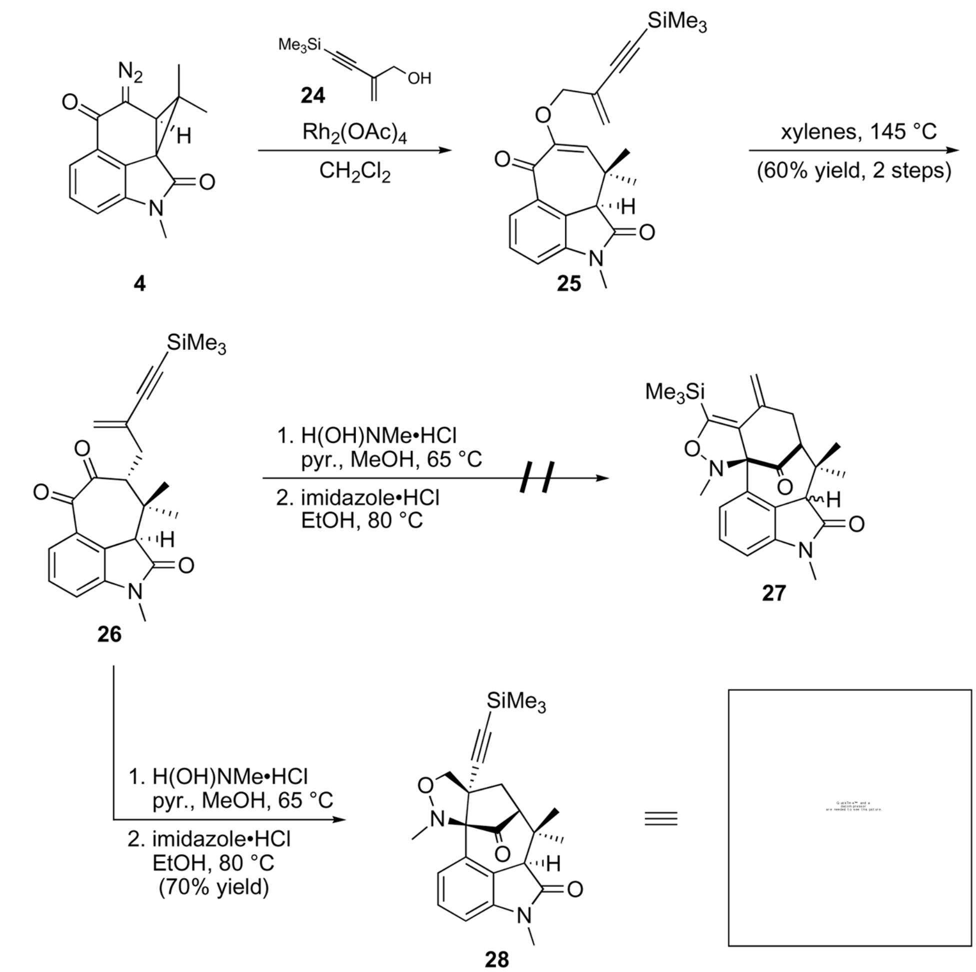


1. H(OH)NBn•HCl
pyr., MeOH, 65 °C
2. imidazole•HCl
EtOH, 80 °C
15
17
(48% yield)
18
(40% yield)

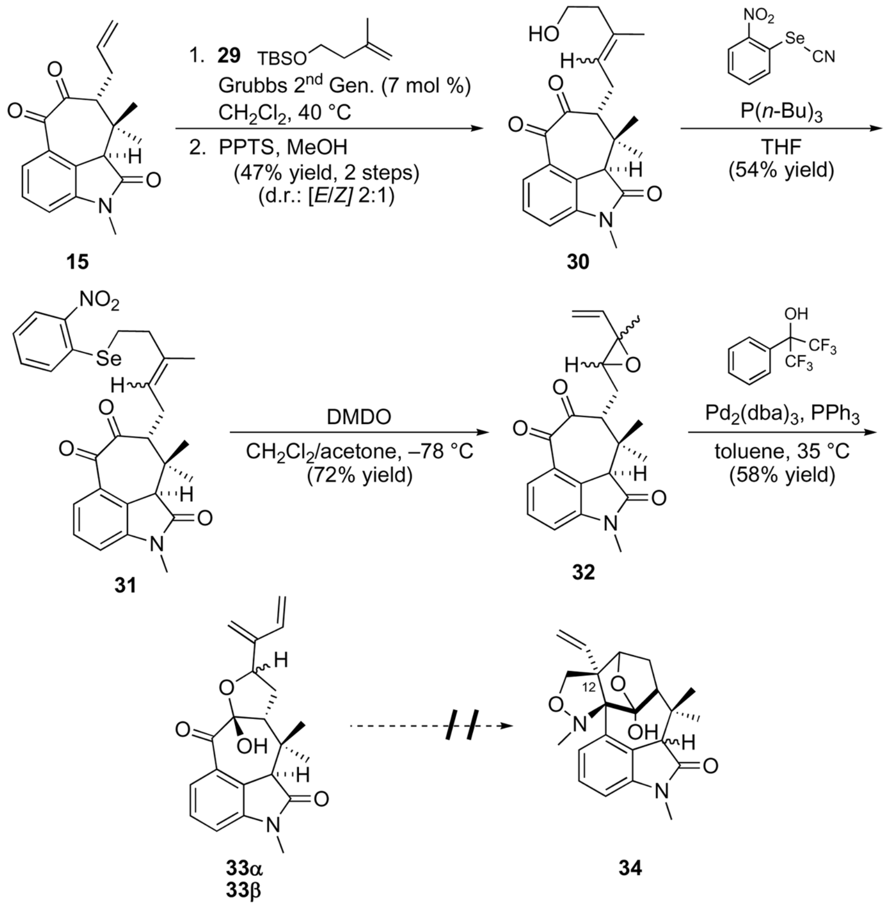
Scheme 4.



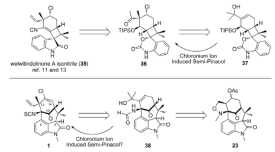
Scheme 5.


4
Me3Si
24
OH
Rh2(OAc)4
CH2Cl2
SiMe3
25
xylenes, 145 °C
(60% yield, 2 steps)
SiMe3
26
1. H(OH)NMe•HCl
pyr., MeOH, 65 °C
2. imidazole•HCl
EtOH, 80 °C
Me3Si
27
1. H(OH)NMe•HCl
pyr., MeOH, 65 °C
2. imidazole•HCl
EtOH, 80 °C
(70% yield)
SiMe3
28

Scheme 6.

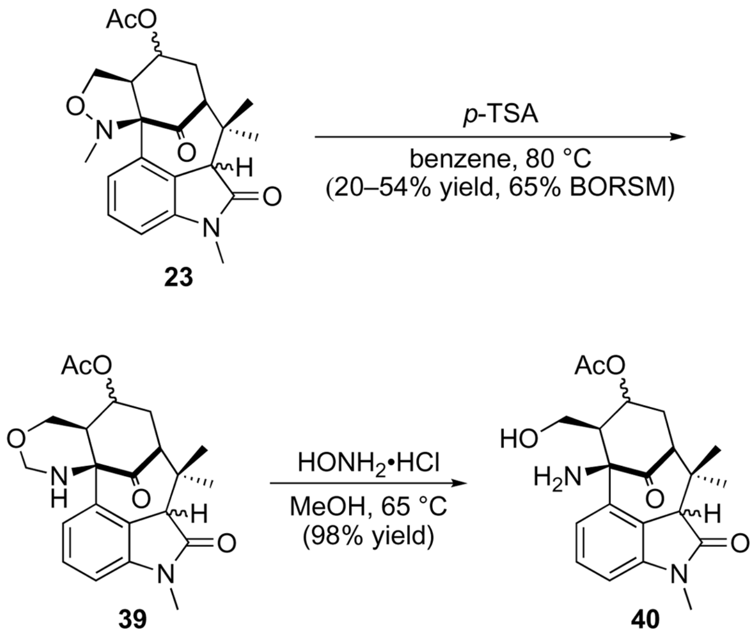

1. 29 TBSO
Grubbs 2nd Gen. (7 mol %)
CH2Cl2, 40 °C
2. PPTS, MeOH
(47% yield, 2 steps)
(d.r.: [E/Z] 2:1)
15
30
HO
NO2
Se
CN
P(n-Bu)3
THF
(54% yield)
31
DMDO
CH2Cl2/acetone, –78 °C
(72% yield)
32
OH
CF3
Pd2(dba)3, PPh3
toluene, 35 °C
(58% yield)
33α
33β
34
12

Scheme 7.

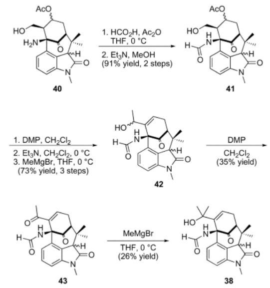


Scheme 8.

NIH-PA Author Manuscript
NIH-PA Author Manuscript

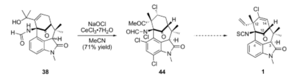

AcO
O
N
O
H
O
N
23
p-TSA
benzene, 80 °C
(20–54% yield, 65% BORSM)
AcO
O
N
H
O
H
O
N
39
HONH2•HCl
MeOH, 65 °C
(98% yield)
AcO
HO
H2N
O
H
O
N
40

Scheme 9.



AcO
HO
H_2N
O
H
O
N
40
1. HCO_2H, Ac_2O
THF, 0 °C
2. Et_3N, MeOH
(91% yield, 2 steps)
41
1. DMP, CH_2Cl_2
2. Et_3N, CH_2Cl_2, 0 °C
3. MeMgBr, THF, 0 °C
(73% yield, 3 steps)
42
DMP
CH_2Cl_2
(35% yield)
43
MeMgBr
THF, 0 °C
(26% yield)
38

Scheme 10.



Scheme 11.